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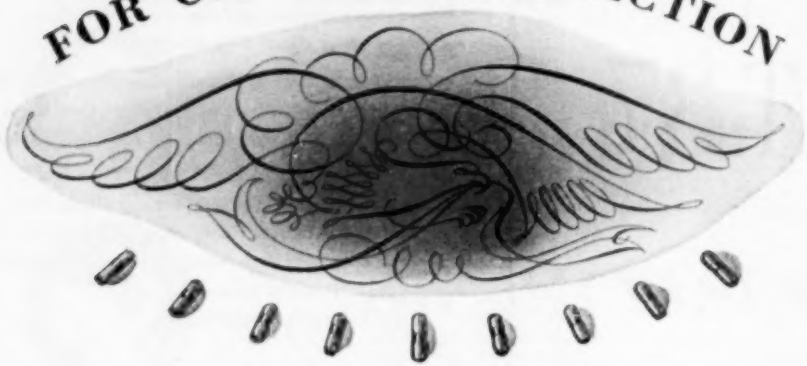

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CONTENTS

EDITORIAL

EUTHANASIA.

PUBLIC interest in the subject of euthanasia has reached a level almost approaching hysteria during the last several weeks. Two cases, in particular, have made the headlines, and one of these involved a physician. A great deal of comment, editorially and otherwise, has been made on this incident. Unfortunately, most people have considered this case generally on an emotional basis with little or no application of logic.

We have no doubt but that what this physician is alleged to have done in terminating the suffering of his cancer patient is done by one means or another almost every day somewhere in the United States. The difference is that, in most instances, the attending physician fails to list his act on the patient's medical record. One wonders just why this specific case was not handled the same way. It would almost appear that the physician in question was seeeking publicity or attempting to become a martyr for a cause which he believed to be just. So much for this individual case. Let us now consider the general problem of euthanasia.

When one examines this problem objectively, it would appear that there are only two bases on which there can be valid objections to euthanasia. In the first place, many who approve it in practice feel that if it were permitted legally such power would be subjected to great abuse. The fear is expressed that with this power physicians might cause the death of certain individuals, not as an act of mercy but in order to eliminate them for some other reason. There does seem to be some basis for this fear. Only a short time ago we witnessed a mass destruction of people by a presumably civilized country for the purpose of "improving the race." With such evidence of the potential brutality of even civilized people, it does seem a risk to permit anyone to wield such power. On the other hand, physicians long have possessed the power to place those judged insane in mental institutions for life, if need be, and there appears to have been little or no abuse of this authority.

The other objection which has been made to euthanasia is on the basis of morality. It has been argued that man should not take away

what he cannot give back, and that since only God can create life, only He should destroy it. One may or may not agree with this logic, but if a person subscribes to it as valid, a very good case can be built supporting such validity. The difficulty lies in the inconsistency with which individuals judge issues, all of which are based upon the same premise. For example, if one objects to euthanasia on a moral basis, he should be consistent and oppose both capital punishment and military service just as strongly. It is just as immoral to cause a criminal to die in the electric chair or for a soldier to kill his enemy as it is to cause the death of one who is suffering from an incurable disease. We have been led to believe that causing death for these reasons is not only proper but actually we reward a soldier with citations and medals, including the Congressional Medal of Honor for his act, provided he kills enough people. Human beings truly are not addicted to the use of logic in the development of their code of behaviour. Undoubteldy, many who read this editorial will be somewhat aroused when we place killing an enemy and killing someone as an act of mercy in the same category. Actually on the basis of Christian principles, the latter act, if it differs at all, is the lesser evil. How few people, however, are sufficiently logical to consider it so.

We are, at present, neither for or against euthanasia, although we do not deny that there are excellent reasons for permitting this practice legally. It does seem, however, that in discussing this problem it would be wise for all of us to think more clearly and with better logic. Too much of what we believe to be right or wrong is not based upon valid and objective thinking. What we have been taught and led to believe has given most of us a number of false notions which we seem willing to defend to the bitter end and with the utmost emotion.

There are many serious social problems including euthanasia, the sterilization of the mentally unfit, birth control, our outmoded penal system, and others. If a scientific logical approach had been given these human problems, such as has been given those of a purely mechanical and physical nature, we of the human race would not be struggling in such a morass in our attempts at social progress.

L. F. Tice

THE ADSORPTION OF ATROPINE ON RESINS

By Miller J. Sullivan and Gustav J. Martin *

Introduction

FOLLOWING the work of Martin and Wilkinson (1) (2), the use of anion-exchange resins for the management of gastric acidity and the treatment of peptic ulcer has become general (3, 4, 5, 6, 7, 8, 9, 10, 11, 12). One possible improvement would be a combination of an anion resin with atropine in a union which might synergistically increase the effectiveness of each. As a further extension of this study the exact conditions necessary for the adsorption of atropine on a sulfonic type cation exchanger were investigated.

Experimental Section

Atropine Sulfate U. S. P. was used without further purification.

Anion Exchange Resin: the anion exchange material was a sample of carefully processed 80-100 mesh polyamine resin supplied by the National Drug Co. under the trade-name "Resinat".

Cation Exchange Resin: The cation exchange resin was commercial amberlite IR-100-H supplied by The Rohm and Haas Co., and it is a typical sulfonic type cation exchange resin. In one series of experiments it was used without further purification. In the other, it was "acid-conditioned" which means that it was stirred for ten minutes each with five portions of 5% hydrochloric acid and then was thoroughly washed.

Experimental Procedure: Ten grams of resin were placed in a beaker and 50 ml. of atropine sulfate solution were added. The mixture was then mechanically stirred at a constant rate for a predetermined time interval and very quickly filtered through a medium sinter. (Filtration required less than one minute since vacuum was used.) Ten ml. of the filtrate were then analyzed by an iodometric method discribed by Thomas and Jatrides (19). This method was found to be convenient for the purpose and was used to determine both the original and final concentrations.

* Research Laboratories, The National Drug Co., Philadelphia, Pa.

Experimental Results: Experiments with "Resinat" are shown in Table I.

Table I

200 grams of "Resinat" per liter. Atropine sulfate concentration 5.41 g/l.

Contact Time, minutes	Atropine Sulfate Adsorbed on Resin mg./g.	Atropine Sulfate Remaining in Solution g./l.	% Atropine Sulfate Removed from Solution
20	9.8	3.46	36.1
40	12.5	2.90	46.2
60	14.9	2.44	55.0

It is particularly to be noted that the observed rate is much slower than might be expected of many ion-exchange processes and probably indicates a somewhat different mechanism.

In Tables II and III are shown some of the results obtained with Amberlite IR-100-H.

Table II

200 g. of Amberlite IR-100-H per liter. Atropine sulfate concentration 5.41 g/l.

Contact Time, minutes	Atropine Sulfate Adsorbed on Resin mg./g.	Atropine Sulfate Remaining in Solution g./l.	% Atropine Sulfate Removed from Solution
20	11.6	3.10	42.8
40	17.4	1.93	64.4
60	21.6	1.08	79.8
	(Resin was increased to 400 g/l.)		
20	13.0	0.22	95.8

Table III

200 g. of Amberlite IR-100-H (acid-conditioned) per liter. Atropine sulfate 5.41 g/l.

Contact Time, minutes	Atropine Sulfate Adsorbed on Resin mg./g.	Atropine Sulfate Remaining in Solution g./l.	% Atropine Sulfate Removed from Solution
10	11.0	3.20	40.9
20	19.1	1.58	70.9
40	26.7	0.07	98.6

It is particularly to be noted that doubling the concentration of the resin approximately doubles the rate of removal of atropine from solution as may be clearly seen from Table II. It is further to be noted that the acid-treatment appears to have caused a large increase in rate as may be seen by comparing the values given for a contact time of forty minutes in Tables II and III.

Biological Experiment

In order to ascertain the possible in vivo application of these adsorption experiments, acute toxicity studies were run with atropine sulfate. The results are given in Table IV.

Table IV

Acute Toxicity of Atropine Sulfate as Affected by an Anion Exchange Resin

Oral Administration—mice

Group No.	No. Mice in Group	No. Dead in Group	Mg./Kg.	L.D.	Time
			Atropine Alone		
1	10	10	1000	100	24 hrs.
2	10	9	1200	90	24 hrs.
			Atropine plus Anion Exchange Resin		
3	10	7	1000	70	24 hrs.
4	10	6	1200	60	24 hrs.
			Atropine plus Tragacanth—no resin		
5	10	10	1000	100	24 hrs.
6	10	10	1200	100	24 hrs.

Resin = 250 mg./cc. in 0.5% tragacanth for suspension. Each mouse received 250 mg. of resin in groups 3 and 4.

The LD-50 reduction resulting from the concomitant administration of an anion exchange resin doubtless indicates adsorption and retention of the atropine in the gastrointestinal tract where it is slowly released and thus does not build up a comparable blood level.

Discussion

The mechanism of adsorption of atropine on a sulfonic type exchanger would seem to be rather straightforward and can be represented by equation (1).

$$RNH_3^+ + R_1SO_3^- \rightleftharpoons RNH_3SO_3R_1$$

where RNH_3^+ would represent atropine and $R_1SO_3^-$ would represent the resin. (It should be pointed out that the above picture does not attempt to represent the true state of affairs on the surface but rather is only a crude device to represent a set of facts.) Both Adamson and Meyers (13) and Bauman and Eichorn (14) have concluded that at high concentrations the rate-determining step for the exchange of ions in this type of exchange resin would be the diffusion of ions in the resin gel structure. At very low concentrations, Adamson and Meyers (13) concluded that the rate-determining step would be the rate of diffusion through a liquid film surrounding each particle whereas Bauman and Eichorn (14) consider that the rate-determining step would be the mass action rate between ions at the surface of the particle. Practical application of such ideas led to a procedure in which rapid and efficient stirring was used and apparent equilibrium could be obtained under a given set of conditions very rapidly.

That the adsorption of atropine on a sulfonic cation exchanger would be possible had been indicated by the work of Appelsweig (15) and of Appelsweig and Ronzone (16) who used a cation exchanger for the recovery of atropine, scopolamine, morphine and similar compounds. Studies by Sussman, Mindler, and Wood (17) reported the use of exchangers for the recovery of totaquine from cinchona bark and scopolamine from the Datura plant.

The adsorption of atropine by an anion exchange resin is however more obscure and the fact that it is rather strongly adsorbed under the experimental conditions is surprising. It has been found that many substances containing a basic amino group are adsorbed rather strongly (18).

Summary

The adsorption of atropine by anion and cation exchange resins is demonstrated. Basic mechanisms of this adsorption are discussed. In vivo studies with atropine sulfate demonstrate the removal of compounds of this type from gastric and intestinal content thus reducing the acute toxicity.

REFERENCES

(1) Martin, G. J., and Wilkinson, J.: *Gastroenterology 6*:315 (1946).

(2) Martin, G. J., and Wilkinson, J.: *Arch. Biochem. 12*:95 (1947).

(3) Kraemer, M., and Lehman, D. J.: *Gastroenterology 8*:202 (1947).

(4) Spears, M. M., and Pfeiffer, M. C. J.: *Gastroenterology 8*:191 (1947).

(5) Kraemer, M., and Siegel, L. H.: *Ninety-Sixth Annual Session, Am. Med. Assoc.*

(6) Kraemer, M.: *Postgraduate Med. 2*:431 (1947).

(7) Kraemer, M.: *Conn. State Med. J. 12*:305 (1948).

(8) Kasdon, S. C.: *New Eng. J. Med. 239*:575 (1948).

(9) Weiss, J.: *Rev. Gastroenterology 15*:826 (1948).

(10) Marks, J. A.: *Rev Gastroenterology 16*:82 (1949).

(11) Weiss, S., Espinal, R. B., and Weiss, J.: *Rev. Gastroenterology 16*:336 (1949).

(12) Weiss, S., Espinal, R. B., and Weiss, J.: *Rev. Gastroenterology 16*:501 (1949).

(13) Adamson, A. W., and Meyers, L. S.: *J. Am. Chem. Soc. 69*:2836 (1947).

(14) Bauman, W. C., and Eichorn, J.: *J. Am. Chem. Soc. 69*:2830 (1947).

(15) Appelsweig, N.: *J. Am. Chem. Soc. 66*:1990 (1944).

(16) Applesweig, N., and Ronzone, S.: *Ind. Eng. Chem. 38*:576 (1946).

(17) Sussman, S., Mendler, A. B., and Wood, W.: *Chem. Ind. 57*:455 (1945).

(18) Martin, G. J., and Alpert, S.: (In Press.)

(19) Thomas and Jatrides: *J. Pharm. Chem. 21*:185 (1935).

THE PRESENT STATUS OF VITAMIN E*

By Sereck H. Fox **

THIS subject has caused much controversy and difficulty to both scientific and commercial endeavor because of its confusing aspects. Clarification of some of that confusion is an intended function of this presentation, but it is realized that in this case at least, clarity may be but relative.

The Vitamin E of Evans, Bishop and Burr presented a reasonably uncomplicated picture before 1930. This Vitamin E was found in the fat fraction of many substances of plant origin and wheat germ oil was heralded as being of drug significance. Vitamin F (so-called) became its close companion in commercial exploitation.

In the succeeding one and one-half decades it was disclosed that Vitamin E was a tocopherol or mixture of tocopherols, that it was an anti-oxidant and was useful in controlling oxidative processes in fats.

It was learned that there were various homologous tocopherols and that alpha, beta, gamma and delta tocopherols existed in natural oils. But alpha tocopherol, the form preponderant in wheat germ oil, was not always preponderant in other natural oils. Certain of these other oils offered greater economic advantage in their utilization than did wheat germ oil. Therefore it became important to increase the alpha ratio in such other oils by chemical means in order that they might be employed as "sources" of alpha tocopherol, the homolog which by all account and up to now was considered of greatest physiologic importance, to the rat at least.

Then interesting reports began to come in of the work of the brothers Shute and their co-workers in London, Ontario. These reports stirred great clinical interest in the cardio-vascular field. This interest caused and still causes a great demand for tocopherol products. Thus a need for concentrating such products arose. The resulting experimental concentrates had peculiar physico-chemical characteristics such that esterification, specifically acetylation became

* In its original form this paper was presented as an address before the Canadian Pharmaceutical Manufacturers' Association at St. Adele en haut, Quebec, on May 30, 1949.

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advisable. Thus evolved the tocopheryl acetates presently available and thus came about those peculiar relationships in biological activity studied by Dr. Philip L. Harris and his associates at Distillation Products Incorporated; and to Hickman, Embree, Harris, *et al.*, should go firm credit for a sound and most important technical accomplishment, whatever the clinical outcome.

Much difference of opinion has arisen over the clinical effectiveness and the human dietary need of tocopherols. *Shute et al.*, employed Vitamin E in the treatment of heart disease, the hypertensive heart, and the rheumatic heart, and reported on the efficacy of the regimen.

But Levy and Boas employed Synthetic Vitamin E in doses of 200 mgms. to 800 mgms. daily in chronic angina pectoris, active angina, myocardial infarction and rheumatic cardiovalvular diseases. They found no clinical evidence to warrant the use of Vitamin E in the conditions named.

Early in 1949 during an International Conference on Vitamin E many investigators reported on the utilization of Vitamin E by both man and animals. Among the many papers presented were the following:

Evan Shute, Wilfred Shute and Arthur Vogelsang presented evidence indicating the value of Vitamin E in the treatment of thrombophlebitis, arteriosclerosis, Buerger's disease, burns, hypertensive heart disease, rheumatic heart disease and diabetes mellitus.

Stritzler of Queens General Hospital reported definite improvement in stasis dermatitis and stasis ulcer on treatment with tocopherols.

Morris Amt and Erwin Di Cyan of New York found clinical improvement in muscular rheumatism and rheumatoid arthritis; treatment with calcium being more satisfactory when preceded by adequate treatment with Vitamin E.

Steinberg of Rochester General Hospital described improvement in primary fibrositis and questionable improvement in Dupuytren's contracture but reported some value in treatment of rheumatic fever. A fair percentage of failures occurred in the latter.

Scott and Scardino of Johns Hopkins reported on treatment of Peyronie's disease with a favorable result after two years in 28.1% of cases.

Scardino and Hudson of Johns Hopkins indicated that one-half their cases of urethral strictures were benefited by tocopherol therapy.

Dowd of the Boston Evening Clinic and Hospital concluded that massive tocopherol therapy (saturation by injection, followed by 600-1000 mgm. daily by mouth) in conjunction with good corrective therapy offers a worthwhile approach to the management of multiple sclerosis.

Among the negative reports were the following:

Travell and associates in a very careful and well controlled study of forty-one patients with heart disease reported an effort to determine the efficacy of tocopherols in reducing chest pain. Here synthetic alpha tocopheryl acetate was used along with a placebo (19 patients each). They concluded that no benefits from tocopherol could be noted and it mattered not if the pain was of cardiac or somatic origin.

Donegan, Messer *et al.* of Duke University reported on twenty-one patients, seven with hypertensive vascular disease alone, seven with hypertensive heart disease and seven with classical, stable angina pectoris all under alternate placebo and tocopherol therapy. These patients were followed monthly from 5 to 20 months by careful history, electrocardiogram, X-ray, and blood tocopherol levels. Blood tocopherol levels were significantly raised but no appreciable subjective or objective benefit was noted.

Guest (Dept. Pediatrics, University of Cincinnati) reported on tocopherol trials in juvenile diabetes mellitus (8 to 17 yrs. of age). No change in pattern of insulin dosage or glycosuria was noted.

Baer, Heine and Gelfoud, Jewish Hospital, Philadelphia, reported on the treatment of a number of cardiac conditions with Vitamin E. In no case could they demonstrate decrease in cardiac failure or show electrocardiographic improvement.

From these and other studies many medical investigators have concluded that there is sufficient evidence to justify further clinical use

of tocopherols in those entities normally grouped under the term "fibrositis," such as rheumatoid arthritis, but considerable doubt has been expressed of their applicability to the problem of heart disease in its various forms.

At the same conference a great mass of data was presented indicating a broad importance of tocopherols as determined in both small and large animal work. The following examples are noteworthy:

Pigmentation of uterus in E deficient rats.
Restoration of vaginal estrus in old rats by alpha tocopherol.
Maintenance of fertility in male rats with alpha tocopherol.
Reduction of experimental dystrophy in small animals.
The effect of tocopherol and tocopherol phosphate in phosphorylation mechanisms.
Inhibition of hyaluronidase by esters of alpha tocopherol.
The Vitamin E effect in protein deficient rats.
Vitamin E and rat blood hemolysis.

In the final analysis it may be shown that man presents a definite and negative species significance in the matter of tocopherol usefulness but from the reports of animal investigations now in hand it would appear that one could postulate an important effect in man perhaps as yet undisclosed.

As a matter of fact, a literature of considerable size already attests the effectiveness of tocopherol in the treatment of the menopause. Flushing, irritability, and headache were greatly reduced or eliminated according to these reports. Vitamin E was given the role of preferred treatment particularly when estrogens were contraindicated.

Based on these premises perhaps is the wide commercial distribution and medical use of tocopherol products presently seen. This has produced a difficult problem from the technical standpoint of product design. This problem has been increased by strong competition in label claims and the differences in physiologic effect of the commonly described isomers, racemic mixtures and their esters as reported by Harris. Technically we have had to resolve the problem of biological equivalents raised by this information.

Harris reported that statistically averaged responses in rat antisterility investigations indicated that:

a. 1 mgm. *d*-alpha tocopherol is equivalent to 1.36 mgm. *dl*-alpha tocopherol. That is, natural alpha tocopherol is more potent than the corresponding synthetic form (racemic mixture), in the ratio of 1.36 to 1.0.

b. Under the conditions of test it was shown that esters of alpha tocopherol isomers are about 1.62 times as active molecule for molecule as the corresponding non-esterified forms.

Thus, by combining these two effects and including the necessary stoichiometry the relationships in Table I may be calculated.

TABLE I

BIOLOGICAL EQUIVALENTS
ALPHA TOCOPHEROLS AND THEIR ACETATES
AFTER P. L. HARRIS AND ASSOCIATES

d-Alpha Tocopherol	1	Milligram
dl-Alpha Tocopherol	1.36	"
d-Alpha Tocopheryl Acetate	.68	"
dl-Alpha Tocopheryl Acetate	.92	"
International Units	.92	

1 mgm. *d*-Alpha Tocopheryl Acetate = 1.47 mgm. *d*-Alpha Tocopherol
1 " " " " = 2.00 mgm. *dl*-Alpha Tocopherol
1 " " " " = 1.35 mgm. *dl*-Alpha Tocopheryl Acetate

The commercial and competitive result of this excellent technical achievement is disclosed in Table II.

TABLE II

VITAMIN E
COMMERCIAL PREPARATIONS
SOURCE AND APPROXIMATE COST RATIO

Label	Material	Approx. Cost Ratio Raw Material Only
100 International Units (100 mgm. *dl*-alpha tocopheryl acetate) "Bio-Equiv."	74 mgm. *d*-alpha tocopheryl acetate from mixed tocopheryl acetates	1.00
100 International Units (100 mgm. *dl*-alpha tocopheryl acetate) "Bio-Equiv."	108.7 mgm. *d*-alpha tocopherol from mixed tocopherols	1.41

Label	Material	Approx. Cost Ratio Raw Material Only
100 International Units (100 mgm. *dl*-alpha tocopheryl acetate)	100 mgm. synthetic *dl*-alpha tocopheryl acetate	1.89
100 mgm. *d*-alpha tocopheryl acetate	100 mgm. *d*-alpha tocopheryl acetate from mixed tocopheryl acetates	1.35
100 mgm. *d*-alpha tocopherol	100 mgm. *d*-alpha tocopherol from mixed tocopherols	1.297
100 mgm. *d*-alpha tocopherol "Bio-Equiv."	68 mgm. *d*-alpha tocopheryl acetate from mixed tocopheryl acetates	0.919
100 mgm. *dl*-alpha tocopherol	100 mgm. synthetic alpha tocopherol	1.89
100 mgm. *dl*-alpha tocopherol "Bio-Equiv."	73.5 mgm. *d*-alpha tocopherol from mixed tocopherols	0.954
100 mgm. *dl-alpha* tocopherol "Bio-Equiv."	50 mgm. *d*-alpha tocopheryl acetate from mixed tocopheryl acetates	0.676
100 mgm. mixed tocopherols	294 mgm. 34% mixed tocopherols	0.649

In order that the significance of the term "alpha tocopherol" be understandable to the physician and to the user it is obvious that a "benchmark" or standard of reference be employed in label declarations of tocopherol products. Such a reference exists in the International Standard of Vitamin E (*dl*-alpha tocopheryl acetate) which by definition affords one biological unit of Vitamin E in each milligram of that substance. Fortunately the Canadian Department of National Health and Welfare with the help of the Canadian

Pharmaceutical Manufacturer's Association has taken an official position in the matter and has made such practice mandatory in Canada. It would appear to be advisable that similar action be taken in the United States.

BIBLIOGRAPHY

(1) Evans, H. M., and Bishop, K. S.: *Science 56*:650 (1922).

(2) Evans, H. M., and Burr, G. O.: *Memoirs of Univ. of Calif. 8*:25 (1927).

(3) Evans, H. M., Emerson, O. H., and Emerson, G. A.: *Jour. Biol. Chem. 113*:319-332 (1936).

(4) Olcott, H. S., and Mattill, H. A.: *Jour. Bio. Chem. 93*:65 (1931).

(5) Bradway, E. M., and Mattill, H. A.: *Jour. Am. Chem. Soc. 56*:2405 (1934).

(6) Todd, A. R., Bergel, F., and Work, T. S.: *Biochem. J. 31*:2257 (1937).

(7) Evans, H. M., Emerson, O. H., and Emerson, G. A.: *Jour. Bio. Chem. 113*:319 (1936).

(8) Karrer, P., and Fritzsche, H.: *Helv. Chim. Acta 21*:1234 (1938).

(9) Vogelsang, A., and Shute, E. V.: *Nature 157*:772 (1946).

(10) Shute, E. V.: *Surg. Gynec. and Obst. 86*, #1, 1-8 (1948).

(11) Vogelsang, A. B., Shute, E. V., and Shute, W. E.: *M. Record 160*:21, 91, 163, 230, 279 (1947).

(12) Harris, P. L., and Ludwig, M. I.: *Jour. Bio. Chem. 180*:611 (1949).

(13) Harris, P. L., and Ludwig, M. I.: *Jour. Bio. Chem. 179*:1111 (1949).

(14) Hume, E. M.: *Nature 148*:472 (1941).

(15) *Annals—New York Academy of Sciences 52*: Art. 3, 63-428 (Oct 31, 1949).

(16) *Canada Gazette*, Vol. LXXXIII, Part ii, P. C. 289, p. 3 (January, 1949).

(17) Hickman, K. C. D.: *Rec. Chem. Prog. 9*:104 (1948).

(18) Hain, A. M., and Sym, J. C. B.: *British Med. J. 2*:8 (1943).

(19) Christy, C. J.: *Am. J. Obst. & Gynec. 50*:84 (1945).

(20) Rubenstein, B. B.: *Fed. Proc. 7*:106 (1948).

(21) Finkler, R. S.: *J. Clin. Endocrinol. 9*:89 (1949).

(22) McLaren, H. C.: *British Med. J. 2*:1378 (1949).

COLORIMERTIC DETERMINATION OF MORPHINE

By Joseph B. Oram

MORPHINE produces a specific color reaction in the presence of ammonium hydroxide, copper sulfate and hydrogen peroxide. Advantage of this property has been taken in devising a rapid, convenient and sensitive procedure, utilizing a photoelectric colorimeter for the determination of morphine sulfate under the proper conditions. The effect of the variables on the development of a stable color has been investigated and the conditions established which will permit the optical densities of the color developed to approximate adherence to Beer's Law.

Morphine produces a pink to red colored solution with the liberation of gases in the presence of ammonium hydroxide, copper sulfate and hydrogen peroxide (2,4). In 1927, L. Magendie (3) suggested a method following this reaction for the determination of morphine in cortex preparations, utilizing the walpole comparator block, allowing the color to develop for a minimum period of time of 10 minutes in the presence of a very small amount of copper sulfate. In 1932, A. D. Rozenfield (5) compared the resulting colors following this same reaction after a minimum period of 15-20 minutes.

Apparatus and Solutions

Instrument: Spectrophotometric measurements were recorded with a Fisher Electrophotometer. A colorimeter lens attachment was used to focus the incident light, and a miniature colorimeter cup holder attachment was used which permitted the use of 10 ml. of solution.

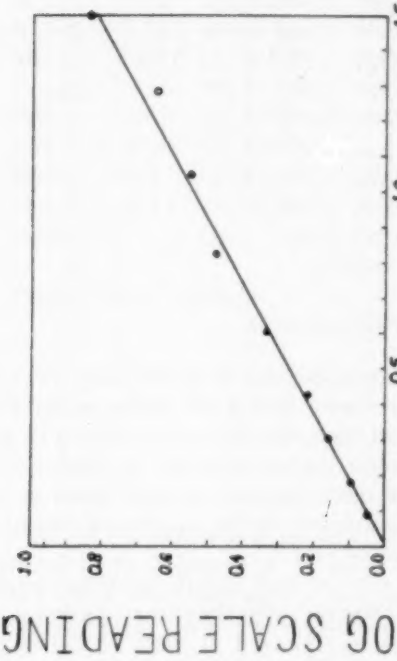
Reagents: Hydrogen peroxide 3%, concentrated ammonium hydroxide, copper sulfate 1.5% aqueous solution.

Standard Solution: A stock solution was prepared containing 1.5 mg./ml. of morphine sulfate. Portions of this stock solution were diluted with distilled water to obtain the necessary working standards.

Standard Reference Curve

To 5 ml. aliquot proportions of the working standards, 0.5 ml. of 1.5% copper sulfate solution, 1 ml. of concentrated ammonium

hydroxide and 1 ml. of 3% hydrogen peroxide were added, and the reaction was allowed to subside slightly. The reactants were placed in a boiling water bath for 5 minutes, cooled and diluted to 10 ml. The optical densities were then recorded at 4250 Å (blue filter) and used to establish the standard reference curve by plotting the logarithmic scale readings of the instrument against the concentration of morphine sulfate (morphine if desirable) in the working standards. A typical curve appears in Figure I. A blank was used in the reference cell.



STANDARD REFERENCE CURVE AT 4250 Å

FIGURE I.

The points as plotted on the standard reference curve were checked over a period of 3 days, and reproducibility was obtained within an average of 0.0025 on the log scale of the instrument as shown by Table I.

Table I. Reproducibility of points on standard reference curve on three consecutive days.

Conc. of morphine sulfate in mg./ml.	Log scale readings per days examined			Average error in reproducibility on log scale in instrument
	1.	2.	3.	
1.500	0.840	0.840	0.860	0.0100
1.280	0.648	0.648	0.650	0.0010
1.050	0.551	0.551	0.552	0.0005
0.830	0.480	0.482	0.479	0.0015
0.607	0.336	0.338	0.335	0.0015
0.427	0.220	0.224	0.218	0.0030
0.307	0.160	0.160	0.165	0.0025
0.180	0.096	0.098	0.095	0.0025
0.090	0.052	0.052	0.052	0.0000
			Average Error	0.0025

This procedure was used on samples of known assay (weighed value of morphine sulfate) over a period of several weeks using freshly prepared solutions and reagents. The error resulting by comparing the determined value of the samples with the known value falls within an average of 0.009 mg./ml. or 3%; however, the percentage error is highly magnified by the smaller concentrations. This is clearly shown in Table II.

The determined assay may be read directly from the standard reference curve or may be computed from the linear equation representing the calibration curve as was used in Table II. If desired the assay value may be reported as morphine by using a simple gravimetric factor.

Table II. Comparison of determined and actual assay values of morphine sulfate in several samples.

Samples	Log readings	Det'd. assay mg./ml.	Actual Assay mg./ml.	Error mg./ml.	Percentage Error
I	0.840	1.580	1.540	0.040	2.6
	0.830	1.560		0.020	1.3
II	0.438	0.824	0.847	0.023	2.7
	0.440	0.827		0.020	2.4
III	0.237	0.446	0.445	0.001	0.2
	0.232	0.436		0.009	2.0
IV	0.165	0.310	0.317	0.007	2.2
	0.160	0.312		0.005	1.5
V	0.140	0.263	0.264	0.001	0.4
	0.140	0.263		0.001	0.4
VI	0.072	0.135	0.135	0.000	0.0
	0.072	0.135		0.000	0.0
VII	0.028	0.052	0.047	0.005	10.0
	0.028	0.049		0.002	4.2
VIII	0.016	0.030	0.035	0.005	14.3
	0.017	0.032		0.003	8.6
			Average Error	0.009	3.2

Experimental

Effect of Time at Room Temperature: In low concentrations of morphine sulfate, the optical densities of the color developed at room temperature do not change with time. However, with higher concentrations of morphine sulfate, the optical densities developed at room temperature do vary with time as shown in Table III.

Effect of Immersion in a Boiling Water Bath: It was found that immersion of the reactants in a boiling water bath for 5 minutes produced fully developed optical densities which remained stable throughout the 120 minute period studied. The concentration of the samples studied in this manner ranged from 0.090 to 1.500 mg./ml. morphine sulfate. The boiling water bath also aids in the removal of gases liberated during the reaction.

Table III. Effect of time at room temperature.

Time in minutes	Log scale readings	
	0.090 mg./ml. morphine sulfate	0.607 mg./ml. morphine sulfate
initial	0.052	0.653
4	0.052	0.649
30	0.052	0.476
50	0.052	0.390
90	0.052	0.340
120	0.052	0.339

Effect of the Concentration of Ammonium Hydroxide: It was found that a basic medium is necessary for this reaction to proceed. The color intensity does not vary with the amount of ammonium hydroxide present in the amounts between 5 to 30%. The author did not investigate the effect of ammonium hydroxide in concentrations over 30%, since concentrations above this value should not be used in the suggested procedure due to the minimum amount of solution required to keep the color intensity at a maximum in low concentrations.

Effect of the Concentration of Hydrogen Peroxide: There must be sufficient hydrogen peroxide present in order to allow the reaction to go to completion since the reaction is believed to be an oxidation reaction (1). When an excess of hydrogen peroxide was present, there was no effect on the optical densities.

Effect of the Concentration of Copper Sulfate: It was found that the sensitivity of the standard reference curve varied with the amount of copper sulfate present in the reaction when the spectrophotometric measurements were recorded at 4250 Å and using distilled water in the reference cell. Using 0.5 ml. of a 1.5% solution of copper sulfate with a solution containing 1.5 mg./ml. of morphine sulfate, the sensitivity increased approximately 1/10 as compared with the use of 0.1 ml. of a 1.5% solution of copper sulfate on the same concentration of morphine sulfate. This is shown in Table IV.

Table IV. Effect of the concentration of copper sulfate.

Ml. of 1.5% copper sulfate	Log scale readings 1.5 mg./ml. morphine sulfate	blank
0.1	0.760	0.016
0.5	0.840	0.018

Filters Used: It was found that a blue filter, 4250 Å, produced the most sensitive standard reference curve of the 3 filters tried. This is clearly shown in Table V.

Table V. Effect of the use of different filters on the log scale readings.

Filter	Log scale readings of different concentrations of morphine sulfate		
	1.028 mg./ml.	0.591 mg./ml.	0.280 mg./ml.
4250 Å (blue)	0.548	0.330	0.155
5250 Å (green)	0.319	0.198	0.110
6500 Å (red)	0.070	0.060	0.050

Effect of Related Alkaloids: It was found that the presence of codeine did not interfere with the color intensity developed under the conditions of the suggested procedure. The acid esters of morphine and apomorphine produced a red color with the reagents used in this reaction, while dionine and codeine did not produce this reaction (1).

Summary

The suggested procedure approximates adherence to Beer's Law and is accurate to an average of 0.009 mg./ml. from 0.090 to 1.500 mg./ml. morphine sulfate. The immersion of the reactants in a boiling water bath for 5 minutes and the accurate measurement of copper sulfate to be added are essential factors in the production of fully developed and stable colors. Acid esters of morphine and apomorphine produce this color action while dionine and codeine do not (1).

Acknowledgment

The author wishes to express his deepest gratitude to Mr. R. F. Muraca whose untiring interest made this paper possible.

REFERENCES

(1) Bamford, F.: *Analyst, 56*:586-9 (1931).

(2) Denige: *Repert. de Pharm., 10* (1911).

(3) Magendie, L.: *Bull. Soc. Pharm. Bordeau, 65*:157-78 (1927).

(4) Oliver: *J. Am. Med. Assoc., 63*:513 (1914).

(5) Rozenfield, A. D.: *Farm. Zhur., 8-9*:243-51 (1932).

BASIC ROLE OF DRUGS IN MODERN THERAPY *

By J. M. Hayman, Jr., M. D.**

WHEN or why man first began to eat certain substances with the hope of curing disease is unknown. The custom must be about as old as man himself, and perhaps older, for some animals will seek out foods when sick that they will not touch when well.

Nor can we tell how much of the ancient use of herbs was based on an inherent belief in magic, and the benefits therefore psychological, and how much was physiological. The doctrine of signatures, which played such a conspicuous part in medical practice in Europe only a few hundred years ago, has its roots in Chinese practice, some 2,000 years before the Christian era. According to this doctrine there is a resemblance either between a plant and the cure of a disease, as preserved in the names "fever wort" and "boneset" or between the plant and the part of the body affected. Some of the 17th century applications of this doctrine are amusing:

"Walnuts have the perfect signature of the head: the outer husk or green covering represents the pericranium . . . whereon the hair groweth, and therefore, salt made of those husks or barks is exceedingly good for wounds in the head. The inner woody shell hath the signature of the skull, and the little yellow skin or peel that covereth the kernel is like the thin scarf that envelops the brain and therefore . . . if the kernel be bruised and moystened with the quintessence of wine and laid upon the crown of the head it comforts the brain and head mightily" (1).

The rational mixtures of many substances in one remedy reached a high point in the famous electuaries and theriaca of the middle ages. Some of these contained from 40 to 60 ingredients. It is no wonder that the most famous, as the Theriaca Andromachi, was believed to be a universal cure-all.

But even at these times there were violent protests against such shotgun mixtures. "The apothecaries are my enemies because I will

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* Delivered at the American Pharmaceutical Manufacturers' Association Scientific Award Ceremony on November 29, 1949 at The Waldorf-Astoria, New York City, New York.

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not empty their boxes," cried Paracelsus . . . "The physician's duty is to heal the sick, not enrich the apothecaries . . . My recipes are simple and do not call for forty or fifty ingredients."

Some ancient customs were not so different from modern practice. The Chaldeans had a very practical method. They exposed a sick member of the household on a litter by the highway in the hope that some passerby might recognize the disease and recommend a cure. Compare the modern practice of advertising medicines along the highways in the hope that those who are ill may recognize the symptoms and purchase the remedy.

Even with pure chemical compounds of known activity we are not free from the fact that much of the benefit derived from their use may be due to the faith of the patient. In his recent book on the treatment of adrenal insufficiency Thorn warns that in using desoxycorticosterone as a screening test for adrenal insufficiency it is necessary to follow a period of drug injection with a period of injection of the vehicle alone in order to determine whether the improvement alleged by the patient can be attributed to the drug (*2*).

Just when the scientific study of drug action began it is difficult to say. Certainly prehistoric man knew that certain plants regularly produced untoward symptoms and others led only to a sense of comfortable distention. The effects of fermented drinks, both good and bad, are recorded in the Bible. The South American Indians knew that dipping their arrows in the juice of strychnos toxifera made them much more effective.

But all of this is very different from the deliberate study of where and how the effect of a drug is produced. The earliest pharmacologists in the modern sense were probably Anton Stoerck (1731-1803) and Purkinje (1787-1869) who studied the effects of camphor, opium, belladonna and turpentine on himself. Garrison calls Francois Magendie (1783-1855) the founder of modern pharmacology (*3*). Magendie's work was carried on by Alexander Crum Brown and Thomas Richard Fraser, the latter being the first to investigate the relation between chemical constitution and physiological action (*4*). Rudolf Buchheim was followed by his pupil Oswald Schmiedeberg, and Schmiedeberg in turn by his pupils Hans Meyer, Cushny and Abel. While this type of pharmacological investigation served a tremendous purpose in forming the basis for a rational therapeutics, and of eliminating, albeit slowly, the great mass of impotent nostrums

from the pharmacopoeias, and less rapidly from the apothecaries' shelf, it of necessity became sterile.

During all these centuries an untold number of substances were tried for any discoverable effect in changing the course of disease. This hit-and-miss type of testing still goes on, and occasionally, as with prontosil, turns up a diamond. But the substances tried out now are usually the results of the ingenuity of the synthetic chemists rather than of nature, and primary trials are conducted on animals or micro-organisms rather than on man. Yet the basic philosophy of trial and error continues essentially unchanged—sulfonamides, antihistamines, antibiotics.

The discoveries in chemotherapy not only provided a number of highly useful and effective therapeutic agents, but shifted the pharmacological emphasis from the "site" of drug action to the inter-related chains of chemical reactions which constitute the dynamic equilibrium of the cell. This came at a time when physiology and biochemistry were also undergoing a revolution in their approach to the study of vital processes, a shift from gross observation of mass mechanical and chemical processes to the intimate life of the cell. Students of these disciplines became less interested in the daily excretion of creatinine than in the inter-relation of enzymes. This opened new fields and vistas for pharmacology and has apparently rescued it as a separate discipline of the medical sciences from the early death from sterility and dry rot which seemed inevitable a few years ago.

At the present time there is much evidence that the action of many drugs and poisons is mediated through a direct or indirect effect on enzyme systems. This is not a new hypothesis, for Myrback made a similar suggestion in 1926 (5). Perhaps the example of greatest importance, at least historically, is physostigmine, which Loewi and Navratil showed specifically inhibited choline esterase (6). It is of considerable practical importance that the rate of hydrolysis of choline esters can be altered by modifying the structure of the choline moiety or of the esterifying acid. But in the present state of knowledge there are many drugs, such as anaesthetics, barbiturates, morphine, amphetamine, whose action cannot be related to any specific enzyme system. The biochemical approach, however, is bound to be fertile. The discovery of the action of BAL (dithiopropanol) in the treatment of arsenic (Lewisite) poisoning was the direct result of studies of the effect of this gas on tissues, and the

discovery that it interfered with cellular life by combining with sulfhydryl groups. It was then eminently logical to expect that a substance with sulfhydryl groups might form a firmer compound with arsenic than the cellular components, and so serve as an antidote.

"The enzymic approach to the study of the mode of action of drugs is by no means limited to those compounds which affect mammalian tissues. The chemotherapy of infectious and parasitic diseases is based on the use of compounds which in suitable dosage have less effect on chemical reactions essential to the well-being of the host than on those reactions requisite to the life or reproduction of invasive organisms" (*7*).

While the virtue of the original prontosil was found by the routine hit-or-miss trial of every conceivable compound, the development of the effective sulfonamide family depended first on a determination of the fate of prontosil in the body and then on the synthesis of related compounds in an effort to diminish mammalian toxicity while preserving antibacterial power. But curiosity as to the mode of action may well turn out to be more important in therapeutics than the industry of the synthetic chemists. Woods and Fildes suggested that the effect of the sulfonamides was due to their substituting for a structurally related compound essential for the life or reproduction of certain bacteria (*8*). This "essential metabolite" appeared to be para-aminobenzoic acid. So, when it was found that animals infected with the rickettsia of typhus fever died more quickly when given sulfonamides than the controls, it was obvious to try para-aminobenzoic acid. Except for these steps in biochemical knowledge, the hit-or-miss trial of para-aminobenzoic acid in typhus fever probably would not have occurred, except by chance, for a hundred years!

This concept that interference with biological processes may result from the use of compounds structurally related to, but not utilizable in place of, substances essential for life or reproduction constitutes a new chapter in pharmacological thinking.

With laboratories equipped to probe the essential biochemical nature of cellular energy, and the organic chemists ready to furnish compounds which will reinforce, modify, or antagonize these processes, why is there still so much discrepancy between the promise of a new drug in the laboratory and its ultimate place in clinical medicine?

Both pharmacologists and clinicians deal with the same biological material. But the pharmacologist can control the age, sex,

breeding, diet and previous health of his experimental animals, while the clinician has to take what is offered in the office, clinic or ward, test subjects of unknown breeding which vary in nutritional state, age, and previous disease.

The pharmacologist, if he wants to, can run adequate control groups. But the influence on the lay mind of the reports of alleged virtues of a new drug in popular magazines makes it very difficult for the clinician to appraise a drug under controlled conditions. Of course, a good many thousand dollars worth will have been sold before the tumult and shouting dies.

There are some reasons for failure of a remedy to become established in the clinic in spite of laboratory promise which are worth reviewing. One of the most obvious is that absorption in man may be very different from the test animal, and moreover varies from person-to-person and even in the same person from time to time. I remember vividly, years ago, attempting to digitalize a decompensated cardiac patient with tincture of digitalis. He was finally taking a dram three times a day without apparent effect. The tincture, apparently, was impotent. But assay by the U. S. P. frog method, then official, showed that it was up to the manufacturer's claim. The patient was subsequently promptly digitalized by the usual amount of another preparation. I have also counted twenty 5-grain cascara tablets in the colon of a patient at autopsy, although tablets from the same bottle seemed to have produced the usual result in the majority of patients on the ward at that time. Of course, I suppose the results in these patients may have been psychic!

The virtue of sulfaguanidine in the treatment of intestinal infections was claimed to be due to its lack of absorption, and that consequently toxic symptoms would not be encountered. This is approximately true in the normal intestine. But when the gut is congested, inflamed, or ulcerated by dysentery or other infectious process, the absorption is greatly increased, so that blood levels may be obtained comparable to those encountered with other, more readily "absorbable" compounds.

Another disappointment to the manufacturer is the development of toxic symptoms of one kind or another with the general use of a drug which were not apparent either in animal experiments or preliminary clinical trial. Rodents cannot vomit. So the absence of gastric symptoms in rats furnishes no assurance that these may not

be prominent in man. That one species of animal may be more readily poisoned by a given amount of drug per kilo than another is well known. But there are marked differences in individuals of the same species, even for a given age and sex. For instance, Dr. Levy, in our laboratory, was unable to establish a satisfactory LD_{50} for rats poisoned by parenteral injection of mercuric chloride until he used animals of the same inbred strain. Consequently, it takes extensive experience with the hybrid human species before the incidence of toxic manifestations can be determined. And to justify recommendation of a new drug, it takes a lot of cures to make up for one dead patient.

Many people died of agranulocytosis before its relation to amidopyrine was recognized. Since this experience physicians have been much more alert to the possibility of leucopenia from any compound containing the benzol ring. Since this toxic manifestation may come on suddenly, after the patient has been taking the drug for months with apparent impunity, even its occasional occurrence diminishes the usefulness of a drug tremendously.

Another type of reaction which diminishes the value of a drug is the development of peculiar skin lesions—fixed drug eruptions—on long continued administration. Atabrine probably furnishes a good example. The effectiveness of atabrine as a malarial suppressive had been established before the war. The yellow color of the skin it produced was well known. This was at most an inconvenience. But the relation of the so-called atypical lichen planus to atabrine was obscure for a long time. What made the analysis more difficult was that fact that a patient with lichen planus who had been off atabrine for months could be given a week's course of the drug for an attack of malaria without any exacerbation of skin lesions. It was only when it was shown that it required an average of three months' administration to produce the lesions that the relationship became clear (9). While the incidence of lichen planus was not great enough to negate the value of atabrine suppression from a military point of view, it made an awful lot of men awfully uncomfortable. One of the advantages of chloroquin was that in preliminary trials it produced no such skin lesions. Yet Alving found that administration of relative large doses for 8 and 12 months gave such lesions in two individuals (10). Whether it is better than atabrine in this respect can only be determined by an experience comparable to that in the last war.

Malaria furnishes another example of why the results of animal and human experience may not agree. A causal prophylactic, that is one that will "cure" malaria, must affect the parasites during their extra-erythrocytic cycle. These extra-erythrocytic forms are found in the cells of the reticulo-endothelial systems in avian malaria, while in monkeys and man they are in the liver cells. There is no reason why a drug should be concentrated equally well in endothelial and hepatic cells. The differences in prophylactic activity of antimalarials in avian and human malaria may be due to this fact or to differences in the metabolism of the parasites (11).

Similarly there is apparently a significant difference in the metabolism of even closely related parasites. The oxidative metabolism of the filarial worm *L. carinii* is strikingly inhibited by certain cyanin dyes, so that infection with this parasite in cotton rats can be almost miraculously cured. The dyes are useless in human infection with *W. bancrofti*, partly due to toxic symptoms but apparently also due to differences in the metabolism of the parasite. For Hetrazan, which appears effective in *W. bancrofti* infections, has only minimal effects on *L. carinii* (12).

The usefulness of many drugs is diminished because of the relative frequency with which reactions classified as allergic develop on continued, and particularly repeated administration. These can rarely be predicted by laboratory studies. The sulfonamides and barbiturates are well known examples. It has been shown in both animals and man that nitrogen balance can be maintained by intravenous injection of protein hydrolysates. Unfortunately, a number of patients for whom this treatment would be most valuable develop fever after 7 to 10 days, presumably as a result of the development of antibodies to the polypeptides in the hydrolysate. The incorporation of penicillin in an oil or wax menstruum to delay absorption is a bright idea, but since certain people are, or become, sensitive to the drug, it could be foretold that some of these would develop a severe, even necrotizing, reaction similar to the Arthus phenomenon where penicillin was injected in such a way that it was not rapidly absorbed.

The relative importance of enzyme systems, and so of drugs that act on these systems may vary in man and other animals. After all, men aren't mice!

Certainly there is evidence that the importance of sympathetic innervation varies in different animals. In the rabbit, the sympathetic

control of the renal circulation seems to be particularly prominent, so that alterations in renal blood flow and volume of glomerular filtrate are readily produced. In this animal, the xanthines usually produce a significant diuresis, and the combination of a xanthine with a mercurial produces a significantly greater effect than the mercurial alone. Such an effect does not occur, and cannot be expected in man and other animals where the xanthines alone are less effective.

In other instances, a drug may have the effects predicted from laboratory study, but the presence of additional effects, often unsuspected, cause disappointment. The drowsiness due to several "antihistamine" drugs is an example. This is of little concern to the patient in bed with the hives, but is of great importance if he is going to drive an automobile.

Drugs have been man's constant companion from the Garden of Eden, or before, and faith in their effectiveness almost as natural to us as religion. The recent development of an understanding of drug action, and of the possibilities of designing new agents to modify physiological processes opens undreamed of possibilities. In these developments, the drug manufacturers have played no secondary role. Much of the future happiness of mankind may be in your hands. But I would remind you that "Life is short, and the Art long; the occasion fleeting, experiment fallacious, and judgment difficult."

BIBLIOGRAPHY

(1) LaWall, C. H.: *Four Thousand Years of Pharmacy.* J. B. Lippincott, Philadelphia, 1927.

(2) Thorn, G. W.: *Diagnosis and Treatment of Adrenal Insufficiency.* C. C. Thomas, Springfield, 1949.

3. Garrison, W. H.: *History of Medicine.* 3rd edition. W. B. Saunders, Philadelphia, 1922.

(4) Fraser, T. R.: "On the Antagonism Between the Actions of Physostigma and Atropa," *Tr. Roy. Soc. Edinburgh, 26*:161, 1869.

(5) Myrback, K.: "Compounds of Some Enzymes with Inactivating Substances," *Z. physiol. Chem., 158*:160, 1926.

(6) Loewi, O., and Navratil, E.: "Uber humorale Ubertragbarkeit der Herznervenwirkung uber das Schicksal des Vagusstoffs," *Arch. ges. Physiol., 214*:678, 1926.

(7) Welch, A. D., and Bueding, E.: "Biochemical Aspects of Pharmacology," *Currents in Biochemical Research.* Interscience Publishers, Inc., New York, 1946.

(8) Woods, D. D., and Fildes, P.: "The Antisulphanilamide Activity of p-Aminobenzoic Acid and Related Compounds," *Chemistry and Industry, 59*:133, 1940.

(9) Bazemore, J. H., Johnson, H. H., Swanson, E. R., and Hayman, J. M., Jr.: "Relation of Quinacrine Hydrochloride to Lichenoid Dermatitis," *Arch. Derm. & Syphil., 54*:308, 1946.

(10) Craige, B., Whorton, C. M., Jones, R., Pullman, T. N., Alving, A. S., Eickelberger, L., and Rothman, S.: "A Lichen Planus-Like Eruption Occurring During the Course of Chloroquine Administration," *J. Clin. Invest., 27*:56, 1948.

(11) Shannon, J. A.: "Screening Tests and the Pharmacologic Appraisal of Prospective Plasmocides," *Proc. 4th Internat. Congress on Tropical Disease and Malaria,* p. 714, Dept. of State, 1948.

(12) Bueding, E.: "Metabolism of Parasitic Helminths," *Physiol. Rev., 29*:195, 1949.

(13) *Hippocrates, Aphorisms.* Tr. by Francis Adams, Wm. Wood Co.

SELECTED ABSTRACTS

Use of Tetraethylthiuramdisulfide in the Treatment of Alcoholics. A. E. Carver. *Brit. Med. J. No.* 4625:466 (1949). A drug which has no curative value in itself but which produces such unpleasant reactions in the human body when alcohol is ingested following the drug that the lure of alcohol becomes easier to resist, has found a place in the medical armamentarium. The drug cannot rectify the defective personality structure of which alcoholism is a symptom but it does help to gain a sober interval during which the process of reorientation can be begun.

The author stated that the drug, tetraethylthiuramdisulfide, seems to interfere with the normal metabolism of alcohol in the body so that unusually high blood levels of acetaldehyde are obtained. The mechanism of this interference is not yet known. However, acetaldehyde is a normal intermediate step in the metabolism of carbohydrates.

This new drug has a prolonged action, lasting for several days, but there is no evidence of cumulative toxic effects in the doses employed. No symptoms arise unless alcohol is ingested. When alcohol is ingested following therapy with the drug a series of typical symptoms arise. First, there appears a flushing of the face and congestion around the eyes. The pulse rises to about 150 per minute but there is little or no increase in blood pressure. Giddiness, hammering in the ears, and headache next appear and there is a feeling of general distress. If the doses of both substances have been large, vomiting follows and the patient feels thoroughly ill. The symptoms appear within 15 minutes after the ingestion of alcohol. The author thoroughly describes the reactions obtained in one severe case of alcoholism.

The usual procedure is to give a small test dose to determine the reaction of the patient. Usually 0.75 Gm. are given at night and repeated the next morning. A small dose of alcohol is given that day. Then if the reaction is not complete in its severity 1 Gm. is given the next night and repeated in the morning. During the following day large doses of alcohol are given so that the patient's reaction is quite severe. In order to obtain an added sense of security a daily oral dose of 0.25 Gm. is usually prescribed for a month after discharge.

Treatment of Nausea and Vomiting of Pregnancy With Dramamine. P. E. Carliner, H. M. Radman, and L. N. Gay. *Science 110*:215 (1949). Nausea and vomiting, the plaguing symptoms of about 50 per cent of pregnancies, is seldom sufficiently severe to cause interruption of the pregnancy but when vomiting occurs it is sometimes sufficiently severe to require hospitalization because of the dehydration. The cause of these symptoms has never been definitely established.

Since Dramamine gave such excellent results in the control of these same symptoms in seasickness the authors made a preliminary study of the effect of this drug on 43 women in whom the administration of pyridoxine both orally and intravenously, thiamine hydrochloride, sedation and psychotherapy had failed to give relief. Dramamine was given to each patient in a dose of 100 mg. three times a day. In seven patients drowsiness and vague subjective muscle tremors caused the dose to be reduced to 50 mg. Within 3 hours Dramamine brought complete relief of the symptoms to 31 of the patients. The other 12 patients obtained no relief. In 10 patients, unbeknown to them, the drug was replaced by a placebo. During the administration of the placebo the symptoms returned but were again relieved as soon as Dramamine was again administered.

Pharmacological Properties Common to Antihistamine Compounds. N. K. Dutta. *Brit. J. Pharmacol. Chemotherapy 4*:281 (1949). Several important and interesting pharmacological properties of the antihistamine compounds Antistine (2-(N-benzylanilinomethyl)-2-imidazoline-HCl) and Benadryl (β-benzohydryloxy-N,N-dimethylethylamine-HCl) were determined by the authors. The anesthetizing effects of these compounds were tested in guinea pigs based upon the number of pricks out of 36 which failed to produce a response following the intradermal injection of the compound. For comparison of effects 1 per cent procaine-HCl brought no response from 30, 0.25 per cent Antistine brought no response from 23.5, and 0.25 per cent Benadryl brought no response from 27.6. At doses preventing 50 per cent of the responses Benadryl was 3.2 and Antistine 2.3 times as potent as procaine. When the response was plotted against the log concentration the curve was linear.

Both of the antihistamine compounds reduced the acetylcholine effects on cardiac and skeletal muscle. A 20.6 per cent reduction in the response of isolated rabbit auricles to electrical stimulation was produced by a 1:1,000,000 concentration of Benadryl. A similar effect was produced by Antistine but it was less persistent. This effect is about twice that of quinidine. In a preparation of isolated rat phrenic diaphragm Antistine and Benadryl increased the degree of contraction by direct stimulation by 20 and 50 per cent respectively, and by nerve stimulation by 20 and 78 per cent respectively. After the application of d-tubocurarine the response to nerve stimulation was abolished but that to direct stimulation was increased as before. The response to preganglionic stimulation resulting in contraction of the nictitating membrane was depressed when the superior cervical ganglion of the cat was perfused with the antihistaminic drugs.

The average gastric secretion response to 2 tests with histamine in 10 chloralosed and atropinized cats were 12.22 and 13.84 cc. of N/20 HCl. In cats given 3 mg. of Benadryl per Kg. between tests the responses were 9.75 and 16.03 cc. of N/20 HCl respectively.

Clinical Evaluation of the Analgesic Potency of Methadone and Its Isomers. J. E. Denton and H. K. Beecher. *J. A. M. A. 141*:1146 (1949). This report, adopted by the Council on Pharmacy and Chemistry of the A. M. A., was based upon a study to determine the analgesic power of *dl*-methadone (6-dimethylamino-4,4-diphenyl-heptanone-3), *l*-methadone, *dl*-isomethadone (6-dimethylamino-5-methyl-4,4-diphenyl-hexanone-3), and *l*-isomethadone as compared to morphine and also the comparative side effects of these compounds.

A group of 429 postoperative patients were used as subjects to evaluate the analgesic power of the drugs. The basis of comparison was an arbitrarily chosen standard analgesic dose, defined as the analgesic dose giving moderate to complete relief of pain in 90 per cent of the trials. The amount of each drug required for this standard analgesic dose was 7 to 9 mg. per 150 lb. of body weight for morphine, *dl*-methadone, and *l*-isomethadone; 4 to 6 mg. for *l*-methadone; and 26 to 30 mg. for *dl*-isomethadone. A possible explanation of the difference between the standard analgesic dose of *dl*-methadone and *l*-methadone is that the dextro-rotatory isomer is inactive while an

antianalgesic action of *d*-isomethadone may account for the difference between *l*-isomethadone and the racemic form.

The side effects of these compounds were evaluated on healthy, ambulatory, young men. An attempt to evaluate the side effects in the postoperative patients was impossible because of the interference of effects from the anesthesia and from surgery. From the results of the study it was concluded that all of the compounds, with comparable analgesic doses, were equally toxic with respect to the production of a long list of symptoms such as nausea, dizziness, dry mouth, warm glow, etc. and the duration of the symptoms, with the exception of *l*-isomethadone which produced less of the important symptom of nausea. All four drugs exerted a depression of the pulse rate and the respiratory rate to a comparable degree. None of the drugs altered the systolic or diastolic blood pressure. The authors emphasized that, although pain may modify to some extent the incidence of side effects, the best criterion of basic pharmacologic action is obtained from healthy subjects.

The Action of Streptomycin and Usnic Acid in Retarding the Development of Tuberculosis in Guinea Pigs. A. Marshak and M. Kuschner. *Pub. Health Rep.* 65:131 (1950). Previously the *in vitro* activity of *Mycobacterium tuberculosis* had been demonstrated. The authors determined to compare the effects of this substance with streptomycin and to test the effect of combinations of these two agents. Ninety-nine guinea pigs were divided into 5 groups. Group I acted as controls, Group II received 20 mg. usnic acid subcutaneously each day for 6 days and then 10 mg. daily for 24 days, Group III received 3 mg. of streptomycin twice a day for 30 days, Group IV received 1 mg. of streptomycin twice a day for 30 days, and Group V received combined therapy the same as that of group II plus that of group IV. This treatment was started the day following inoculation with 0.02 mg. dry weight of a virulent culture of tubercle bacilli. All of the animals were sacrificed 41 to 44 days after inoculation and the lungs, liver and spleen examined macroscopically and microscopically for lesions as an indication of the extent of the development of the disease. The authors stated that they felt that the liver and spleen were the better organs for assaying the severity of the disease.

No appreciable retardation of the development of the disease was observed in the group receiving usnic acid alone and the group receiving 2 mg. of streptomycin daily. However, retardation was observed in the group receiving 6 mg. of streptomycin a day and in the group receiving the combined therapy. By way of comparison, the percentage of animals listed as having no disease or minimal based on examination of the liver was 26.3 in group I, 10 in group II, 85 in group III, 40 in group IV, and 93.5 in group V. Thus it would seem that a definite synergism exists between streptomycin and usnic acid in the treatment of this disease.

The authors suggest one mechanism of action which may have a bearing on the action of these drugs, although they admit that this system may not have a direct bearing on the bacteriostatic or bactericidal action of either drug. It has been shown that streptomycin forms a complex with desoxyribonucleic acid but it does not interfere with the splitting of the acid by desoxyribonuclease. On the other hand usnic acid will inactivate desoxyribonuclease. This action on the same cellular system may account for the synergistic action of the two substances.

The Treatment of Pulmonary Tuberculosis With Para-Aminosalicylic Acid and Streptomycin. Medical Research Council. *Brit. Med. J.* No. 4643:1521 (1949). The thought that another bacteriostatic agent administered in conjunction with streptomycin might prevent or inhibit the development of resistance, which occurs so regularly after five weeks or so of treatment led to the clinical trials in which *para*-aminosalicylic acid was combined with streptomycin. The preliminary report by the Medical Research Council gave encouragement that this major disadvantage of the use of streptomycin in the treatment of tuberculosis may be overcome or improved.

One type of case was chosen for the study, namely, the acute rapidly progressive bilateral type of pulmonary pneumonia, of recent development, unsuitable for collapse therapy as found in young adults between the ages of 15 and 30. The patients were separated at random into three groups and treated for 3 months. One group received 20 Gm. a day of the sodium salt of PAS, a second group re-

ceived 1 Gm. a day of streptomycin, while a third group received combined therapy in the same amounts of the two drugs.

The results obtained from this study showed that in this well-defined type of case of pulmonary tuberculosis, and at the large dosage of PAS employed, the combination of PAS and streptomycin unequivocally reduced the development of streptomycin-resistant strains of tubercle bacilli during six months following the beginning of treatment.

Use of Triethylene Glycol Vapor for Aerial Disinfection. W. J. Lester, S. Kaye, O. H. Robertson, and E. W. Dunklin. Presented before the annual meeting of the Am. Public Health Assoc. in New York Oct. 28, 1949. Minute quantities of triethylene glycol vapor have been shown to be effective for aerial disinfection as a means of preventing the spread of infections which are air-borne. A wide range of infectious agents, both bacterial and viral, have proven susceptible to this method of disinfection. In the concentrations used no toxic effects have been observed on human beings.

The optimum concentration of the glycol for aerial disinfection is between 2 and 5 micrograms of glycol per liter of air within a 20 to 50 per cent range of relative humidity. To be effective the concentration of the glycol and the humidity must be rather carefully controlled. A lowering of either the humidity or the concentration of the glycol markedly lowers the germicidal action. Triethylene glycol must constantly be replaced in the air, for a portion of the glycol vapors are condensing from the air at all times, and the diluting effect of ventilation also makes necessary the addition of glycol vapor. Vaporizing units should be designed to have an output of at least 0.5 Gm. of triethylene glycol per hour per 1000 cubic feet of air to be treated, according to the authors. Since heat is used to vaporize the glycol in these units the authors add a warning relative to guarding against decomposition of the glycol and fire hazards.

BOOK REVIEWS

The Essential Oils. Vol. II. Ernest Guenther and Darrell Althausen, xiii, 852 pages, including index. D. Van Nostrand Co., Inc., 250 Fourth Ave., New York, N. Y., 1949. Price, $10.00.

Volume II of this important and authoritative work is devoted to the constitutents of the essential oils. Drs. Guenther, Althausen, and Frances S. Sterrett, all of whom are connected with the firm of Fritzsche Brothers, Inc., are designated as the "Authors of Chapters."

The authors state in the preface to the present volume that succeeding volumes of this series will deal with individual essential oils and their chemical composition. They give credit to the classical treatise of Gildemeister and Hoffmann, "Die Ätherischen Öle", 3rd edition for some of the older data presented. The original classification of constituents employed in the latter treatise has been extended to include two additional classes, viz., quinones and furans. In addition, the literature has been exhaustively covered and brought up to date, though it is stated that in some instances only abstracts of papers which were published in foreign journals were available.

The following classes of constituents are considered: (1) hydrocarbons, (2) alcohols, (3) aldehydes, (4) ketones, (5) phenols and phenol ethers, (6) quinones, (7) acids, (8) esters, (9) lactones, coumarins, and coumarones, (10) furan derivatives, (11) oxides, and (12) compounds containing nitrogen and sulfur. The discussion of these requires 768 pages, of which the last 26 are devoted to a separate consideration of certain terpenes, sesquiterpenes, and derivatives thereof, the constitution of which is unknown.

A typical monograph for a constituent of known structure presents the following data: molecular and structural formulas, molecular weight, occurrence, method of isolation, means of identification, physical properties, and use. The literature references pertaining to each compound are conveniently located at the end of each monograph. Frequently further citations are provided under the heading "Suggested Additional Literature."

For purposes of identification, the preparation of derivatives of the various constituents of the essential oils is covered in considerable detail by Dr. Sterrett on pages 769-833. This material is intended to be supplementary to Part VII of Chapter 4 in Vol. I of this work. Directions are provided for preparing appropriate derivatives of hydrocarbons, alcohols, adlehydes and ketones, phenols and phenol ethers, acids, esters, and lactones and anhydrides. The literature references cited in this section include some papers published as recently as 1948.

Dr. Guenther and his collaborators have made a most significant contribution to the literature on the volatile oils, and as each volume of the series becomes available it definitely constitutes a "must" for all workers in this field.

A. A. Dodge

The Official Preparations of Pharmacy. By Charles Oren Lee, Ph.D. Illustrated. St. Louis. The C. V. Mosby Company. 1949. 528 pp. $5.50.

This is a new textbook written for the purpose of explaining chemical and pharmaceutical problems relating to the preparations of the Pharmacopeia and the National Formulary. The preparations are divided into several classes, the smaller and related classes grouped together, but larger classes constitute individual chapters. This grouping follows the generally accepted plan of presenting the simpler aqueous preparations first and gradually advancing to more complicated procedures requiring more skill. The author states in the preface that "The student should have had at least a one-term course dealing with the fundamental principles of the sciences basic to an understanding of pharmaceutical processes." The Pharmacopeia and the National Formulary list formulas and procedures; this textbook discusses many details of procedures, explains basic principles, and in many instances gives the chemical equation for the reactions occurring in many preparations. The student must be ever mindful that there are definite reasons for the official procedures, and he will find the theoretical aspects well explained and the practical information most useful.

The book is clearly arranged and well indexed.

However, it seems to this reviewer that certain statements are unnecessary, such as for example, enumerating the tinctures made with an alcoholic, hydro-alcoholic, or any other menstruum. A similar statement in the chapter on the preparation of extracts seems also superfluous; here reference is made to the number of extracts prepared by certain processes.

The relatively brief discussion of medicinal soft soap could have been more comprehensive. The Pharmacopeia makes specific statements as to the saponification value and iodine value of oils which may be used in the manufacture of medicinal soft soap. This sentence needs to be considered in a textbook of this kind. No attempt is made to explain the necessity for oleic acid in this preparation.

The reviewer has had occasion to refer to several chapters and has found them useful for the student to supplement his lecture notes. A great advantage of this book is that the printing itself is very clear and well-spaced. Its size is convenient so that it can be easily handled. It should serve well as a text for pharmaceutical preparations.

ELSA EHRENSTEIN

Pharmaceutical Compounding and Dispensing. By Rufus A. Lyman and George Urdang. Prepared by 11 authors. 321 pages incl. index. J. B. Lippincott Co., Philadelphia, London and Montreal. Price $6.50.

This is the third in the series of books prepared under the general title "American Pharmacy." The actual authors comprise eleven men closely connected with pharmacy and, in most instances, teaching in the field.

The titles of its twelve chapters give an indication of its scope. They are:

I. Dispensing Through the Ages
II. The Prescription
III. Accuracy in Dispensing
IV. Dosage Forms
V. Dermatologic Pharmaceuticals
VI. Solutions

VII. Solubility
VIII. Incompatibility and the Incompatibilities of Inorganic Compounds
IX. Incompatibilities of Organic Compounds
X. Prescription Packages and Labels
XI. Prescription Pricing
XII. Interprofessional Relations

Each chapter seems to have been prepared with care by an author well qualified to write as an expert on his assigned subject.

The chapters, in some cases, seem more like monographs than the individual chapters of a book since the style and educational level of the material presented varies widely from chapter to chapter. Some of the subjects are discussed in a very practical manner as one would expect in a text on compounding and dispensing. Others, notably the chapter on Solubility, are excellently done but it is very doubtful whether undergraduate students could be expected to follow the rather complex theoretical considerations involved.

A few minor errors are made throughout the text such, for example, as the consistent mispelling of the term quaternary which appears as "quarternary". Some of the examples of prescriptions given are poor representatives of prescription writing, although they may be some actually taken from prescription files. The authors are to be complimented on their individual contributions but there appears to be a lack in overall planning and editing of the book by the editors.

The book should prove a very useful reference for teachers and students of pharmacy as well as others interested in the subject. There is no similar book devoted to this specific material which is more suitable for the purpose.

L. F. Tice

Zinsser's Textbook of Bacteriology, 9th Edition. xl + 992 pages including index, Appleton-Century-Crofts, Incorporated, New York. 1948. $10.00.

The 9th Edition revised by a group of well known scientists eminent in the field of Bacteriology and allied sciences, represents a book which covers both, the theoretical as well as the experimental side of the subject.

The arrangement of the text is much the same as that used in the previous editions, but there are included some new sections such as those on antibiotics and on pleuropneumonia-like organisms. The completeness of the work is apparent from the great number of references to original papers, American as well as foreign, at the end of each chapter. These not only serve as contributory reading, but they are very helpful for any one trying to locate information for the particular subject. The clarity of style and the numerous illustrations make the book a great help not only to bacteriologists but also to students who are none too familiar with the subject.

C. Sideri

Laboratory Outline for General Zoology. By George E. Potter. The C. V. Mosby Co., St. Louis, Mo. Second Edition, 1949. 289 pages.

This manual is planned and arranged to be used in conjunction with George Potter's *Textbook of Zoology* but may be used with almost any textbook, or none. The manual is very complete, it has good coverage on both invertebrate and vertebrate animals. Emphasis is on invertebrates as two-thirds of the book testifies. There are descriptions and laboratory drawings, for example, of three types of protozoa, five types of coelenterates, three flatworms, two annelids, two echinoderms, three mollusks, and four arthropods. Vertebrate emphasis is on the frog but the book also includes study of amphioxus, perch, rat, cat and even on the human skeleton.

Much thought has been given to the usefulness of the book by both teacher and students. The first time technical words are used they are all italicized to aid the student in recognizing them. All the pages are perforated so that they may be removed from the manual, the drawing can be turned in separately for grading or pages can be arranged in a separate notebook. The manual has been published by the planograph method. The drawings are very lightly printed so that they may be traced over with pencil or pen and the final drawing has a neat coherent appearance not found with older and darker printed drawings. In all phases it is a very good manual and answers the needs of laboratory courses with rather short periods and where the need for partial drawings is present.

F. M. White

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